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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,484	CHOO ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7,8,10,11,13-15,21-26,31,34,35 and 38-48* is/are pending in the application.

4a) Of the above claim(s) *1,2,4,5,7,8,10,11,13-15,21-26,31,35 and 38-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 14 August 2006 in response to the Non-Final Office Action mailed 18 April 2006. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 35 and 38-47 were withdrawn from consideration and claims 34, 48 and 49 were considered in the 18 April Office Action. Claims 1, 2, 21, 22, 24, 31, 35, 38-40, 46, 47 and 48 were amended and claim 49 was cancelled in the 14 August Paper. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 34, 35 and 38-48 are pending and claims 34 and 48 are under consideration.

Response to Amendment and Arguments

Rejection of claim 49 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 112

Rejection of claims 34 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of, "non-naturally occurring Cys2-His2 zinc finger binding domain" is **withdrawn** in view of the amendment of the claim to remove the phrase.

Claim Rejections - 35 USC § 102

Rejection of claim 48 under 35 U.S.C. 102(b) as being anticipated by Liden *et al.* (1997) *J. Biol. Chem.* 272:21467-21472 as evidenced by McEwan *et al.* (1996) *BioEssays* 19:153-160 (previously made of record) and Bledsoe *et al.* (2002) *Cell* 110:93-105 is **withdrawn** in view of

the amendment of the amendment of the claim such that either the first or second polypeptide comprises an engineered Cys2-His2 zinc finger binding domain.

Claim Rejections - 35 USC § 103

Rejection of claim 34 under 35 U.S.C. 103(a) as being unpatentable over Vegeto *et al.* WO 93/23431 as evidenced by McEwan *et al.* (*supra*) and Bledsoe *et al.* (*supra*) in view of Liu *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5525-5530 is **withdrawn** in view of the amendment of the claim such that it is now directed to a heterodimer.

Claim 48 **stands rejected** under 35 U.S.C. 103(a) as being unpatentable over Vegeto *et al.* WO 93/23431 as evidenced by McEwan *et al.* (*supra*) and Bledsoe *et al.* (*supra*) in view of Liu *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5525-5530 for the reasons set forth in the 18 April Office Action and herein below in the response to Applicant arguments.

As stated in the 18 April Office Action, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the molecular switch of Vegeto *et al.* to include the engineered polydactyl Cys2-His2 zinc finger DNA binding domain of Liu *et al.* Motivation to combine these teachings comes from the nature of the problem to be solved by the molecular switch of Vegeto *et al.*, which is to regulate expression of a nucleic acid in mammals (*Id.*) and from the teachings of Liu *et al.* that: a) specific delivery of a DNA-binding protein to a single site within a genome as complex as that found in humans, 3.5 billion bp, requires an address of at least 16 bp (p. 5525, bridging col. 1-2); b) although natural proteins containing long polydactyl arrays of zinc-finger domains have been inferred from sequence, no zinc-finger

proteins have been demonstrated to bind such a long contiguous DNA sequence (p. 5525, bridging col. 1-2); and c) the polydactyl proteins described therein can bind to a contiguous 18-bp DNA sequence with high affinity and specificity and function in human cells to activate or repress transcription. Viewed as a whole, the skilled artisan would clearly be motivated to substitute the polydactyl DNA binding domain of Liu *et al.* for the DNA binding domains contemplated by Vegeto *et al.* for construction of a molecular switch operative in mammalian cells to obtain the expected benefit of highly specific delivery of the switch in the complex mammalian genome.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings in view of the modular nature of steroid hormone receptor proteins (see especially Vegeto *et al.*, p. 2, ¶1) and the demonstration by Liu *et al.* that the DNA binding domains disclosed therein can be fused to heterologous polypeptides and are active in mammalian cells (see especially Figure 1 and the caption thereto).

Response to Arguments

In response to the *prima facie* rejection, Applicant disagrees that the problem solved by Vegeto's disclosure required the ability to uniquely address a single site in a mammalian genome. Applicant states that Vegeto makes clear that modified steroid receptors are used in conjunction with heterologous sequences and all of Vegeto's disclosure relating to the use of modified steroid receptors for regulation of gene expression is directed to regulation of exogenous genes. Applicant contends, based on this, the invention of Vegeto does not require the ability to address a single site in a mammalian genome.

This argument has been fully considered but is not deemed persuasive. First, it is noted that for motivation under 35 USC §103 it is not necessary that the product of the primary reference "require" the element disclosed in the secondary reference. All that is necessary is that one of ordinary skill would perceive a benefit in modifying the products taught in the prior art so as to obtain a product having the properties of the claimed invention[1]. As stated in the previous Office Action and reiterated herein above, Vegeto et al. is teaching using the molecular switches disclosed therein to regulate expression in mammals (i.e. in the context of a mammalian genome) and Li et al. teaches that the engineered zinc finger domains disclosed therein advantageously provide highly specific delivery of a switch even in the complex context of a mammalian genome. Although applicant is correct in pointing out that the teachings of Vegeto relate to regulation of exogenous genes, the regulation is to be carried out in mammals (see the 18 April Office Action p. 12, ¶3 and the teachings cited therein) and therefore in the context of the complete mammalian genome. The skilled artisan would perceive the benefit of specificity (i.e., avoiding artifacts due to off target expression) even if the switch of Vegeto et al. does not strictly require the use of a polydactyl zinc finger for operability.

[1] "The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination." (MPEP 1144 citing, *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).) See also *In re Fulton*, 73 USPQ2d 1141 (Fed. Cir. 2004), wherein the Court responded to Appellant's argument that the Board's finding of a motivation to combine lacks substantial evidence because the Board failed to demonstrate that the characteristics disclosed in the secondary reference are preferred over other alternatives disclosed in the prior art stating, "This argument fails because our case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention. '[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination,' not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." (P. 1145, citing *In re Beattie*, 974 F.2d at 1311.)

Next, Applicant contends that replacing the DNA-binding domain in Vegeto's mutant receptor with Liu's zinc finger protein would generate a non-functional product because the dimeric steroid receptor would have to bind to a 36-nucleotide sequence and the probability of such a specific sequence occurring in a mammalian genome is extremely low.

This argument has been fully considered but is not deemed persuasive. As Applicant points out in p. 11, ¶ 3 of the 14 August Paper, "Vegeto's disclosure relating to the use of modified steroid receptors for regulation of gene expression is directed to regulation of exogenous genes..." Because Vegeto is interested in regulation of exogenous genes, the binding site for the molecular switch can be engineered to contain any nucleotide sequence, including a 36-nucleotide sequence recognized by a dimer of two proteins comprising polydactyl zinc finger binding domains. In other words, because Vegeto is teaching introducing an exogenous nucleic acid comprising the binding site into the mammalian genome, there is no requirement that the binding site already exist in the genome. In fact, the very low probability of the binding site occurring naturally even in the mammalian genome is precisely the advantage that would motivate one of skill in the art to use the zinc finger domains of Liu et al.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §112, first paragraph, as obvious over the art.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 34 is rejected under 35 U.S.C. 102(b) as being anticipated by Barbas et al. (1995) WO 95/19431.

Claim 34, as amended, is directed to a complex comprising: (a) a heterodimer comprising (i) a first polypeptide, and (ii) a second polypeptide; and (b) a ligand, wherein the first and second polypeptides bind to DNA, and further wherein the first or second polypeptide comprises an engineered Cys2-His2 zinc finger binding domain.

It is particularly noted that the amended claim no longer requires that the first polypeptide bind to the second polypeptide in a manner modulatable by a ligand as recited in the previously examined claims. Furthermore, the specification states at p. 49, ll. 1-2, "A ligand according to the invention is typically any molecule capable of binding to any of the other components of a switching system." Thus, the amended claim now embraces any complex comprising a heterodimer comprising a first and second DNA-binding polypeptide and anything that binds to either one of the first and second polypeptide (irrespective of whether binding of the first and second polypeptide is modulatable by the ligand), wherein either the first or second DNA-binding polypeptide comprises an engineered Cys2-His2 zinc finger binding domain.

In Example 12 (beginning at page 85), Barbas et al. teaches construction of a Zif$(C7)_6$-Jun/Zif-268-Fos heterodimer, which comprises a C7-type zinc finger linked to a Jun leucine

zipper protein interaction domain and a Zif268 zinc finger linked to a Fos leucine zipper protein interaction domain. As described in Example 10, the C7 zinc finger is an engineered zinc finger DNA binding domain derived from the Zif268 Cys2-His2 zinc finger. (See also Figure 8A and the caption thereto (showing the Cys2-His2 structure of Zif268 finger 1) and Figure 9 and the caption thereto (showing the modification comprised by the C7 zinc finger (leftmost column)). Thus, Barbas et al. teaches a complex comprising a heterodimer comprising first and second DNA-binding polypeptides, wherein at least one of the polypeptides comprises and engineered Cys2-His2 zinc finger DNA binding domain. On page 1, ¶4, Barbas et al. teaches that zinc finger domains are folded around a zinc ion. As the zinc ion is bound to the first and second protein moieties, zinc is a ligand according to the broadest reasonable interpretation of the claim limitation. Thus, the heterodimer of Barbas et al. comprises all of the elements of the complex claimed in the instant application. Therefore, the claimed invention is anticipated by Barbas et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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